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Protracted Radiation Exposure and Cancer Mortality in the Techa River Cohort

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In the 1950s many thousands of people living in rural villages on the Techa River received protracted internal and external exposures to ionizing radiation from the release of radioactive material from the Mayak plutonium production complex. The Extended Techa River Cohort includes 29,873 people born before 1950 who lived near the river sometime between 1950 and 1960. Vital status and cause of death are known for most cohort members. Individualized dose estimates have been computed using the Techa River Dosimetry System 2000. The analyses provide strong evidence of long-term carcinogenic effects of protracted low-dose-rate exposures; however, the risk estimates must be interpreted with caution because of uncertainties in the dose estimates. We provide preliminary radiation risk estimates for cancer mortality based on 1,842 solid cancer deaths (excluding bone cancer) and 61 deaths from leukemia. The excess relative risk per gray for solid cancer is 0.92 (95% CI 0.2; 1.7), while those for leukemia, including and excluding chronic lymphocytic leukemia, are 4.2 (CI 95% 1.2; 13) and 6.5 (CI 95% 1.8; 24), respectively. It is estimated that about 2.5% of the solid cancer deaths and 63% of the leukemia deaths are associated with the radiation exposure.

INTRODUCTION

The Extended Techa River Cohort (ETRC) includes about 30,000 people who received significant low-dose-rate protracted exposures to ionizing radiation as a consequence of the release of radioactive material into the Techa River during the initial years of operation of the Mayak nuclear weapons facility in the Southern Urals. Releases occurred from 1949 through 1956, with the maximal releases in 1950 and 1951. Doses received by cohort members resulted from a combination of external γ-ray exposures arising from contaminated river sediments and flood plains together with internal exposures, resulting largely from the consumption of water, milk and food products that contained ^{137}Cs, ^{90}Sr and other radionuclides. While limited follow-up of exposed individuals was initiated in the 1950s, efforts to develop useful dose estimates and systematically ascertain deaths in a well-defined cohort began in the late 1960s and early 1970s. Information about the Techa River cohort was published in the open literature in the early 1990s (*1–6*). Over the last decade, major improvements in the follow-up of the study population (*7*) and dosimetry have been made (*8, 9*).

This report provides the most detailed information to date on the risks of radiation-associated solid cancer and leukemia mortality among members of the Techa River cohort. Because of the nature of the exposed population (a representative sample of men and women of all ages) with a broad range of individual doses and comprehensive mortality follow-up, the ETRC provides one of the best opportunities to obtain quantitative estimates of the long-term health risks associated with chronic radiation exposures. As highlighted in this report, recent changes in dosimetry have led to increases in cancer mortality risk estimates relative to those based on earlier dose estimates. While the changes in individual dose estimates are well-justified and represent real improvements, questions about certain aspects of the dosimetry have been raised recently (*10, 11*). Thus additional refinements in the individual dose estimates are needed before these preliminary risk estimates can be taken at face value in general assessments of radiation risks.

METHODS

Cohort Definition

The ETRC includes two groups of Techa River residents, all born prior to January 1, 1950, being followed by the Urals Research Center for Radiation Medicine (URCRM). One subgroup of the ETRC, the original Techa River Cohort, consists of people resident in one of 41 riverside villages any time during the period of maximal releases (1950 through 1952). The other subgroup consists of ''late entrants'', that is people who first came to live in one of the riverside villages between January 1, 1953 and December 31, 1960. As described elsewhere (*3–5, 7*), these popu-

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TABLE 1
Follow-up Status for the Extended Techa River Cohort as of December 31, 1999

	Extended catchment area residents		Distant migrants[a]		Total	
Vital status	People	Percentage	People	Percentage	People	Percentage
Alive January 1, 2000	8,470	33%	1,424	34%	9,894	33%
Dead	14,380	56%	861	21%	15,241	51%
Cause known	*12,732*	*89%*	*221*	*26%*	*12,953*	*85%*
Lost to follow-up[b]	2,841	11%	1,897	45%	4,738	16%
Total	25,691		4,182		29,873	

[a] Distant migrants are treated as lost to follow-up from the date of migration from the extended catchment area, which means that the total lost to follow-up is 7,023 (4,182 distant migrants and 2,841 lost to follow-up among extended catchment area residents) as of December 31, 1999.

[b] Last known to be alive prior to December 31, 1999 and treated as lost to follow-up from date of last known vital status.

lations were identified from various official documents (including taxation, vital statistics, and medical records) between the late 1960s and the 1980s. When the Techa River Cohort was initially created, it included 31,234 people. Over the past 10 years, efforts have been made to refine the cohort definition and improve the completeness and quality of the mortality follow-up. As a result of these continuing refinements, the ETRC now includes 29,873 people: 24,988 original Techa River Cohort members and 4,885 late entrants. The reduction is primarily due to elimination of redundant records for people included in the roster under more than one name and of people whose residence histories are inadequate for person-year or dose computation.

About 60% of the cohort members are women and 20% are identified as being of Tartar or Bashkir ethnicity. About 40% of the cohort members were under age 20 at the time of initial exposure and only 30% were over age 40. Women make up 50% of the under age 20 group and almost 70% of the over age 40 group.

Mortality Follow-up

Mortality follow-up for the original Techa River Cohort members begins on the latest of January 1, 1950 or the date they came to live on the Techa riverside, while follow-up for late entrants begins at the time they came to live on the Techa. For this report, follow-up continues until the earliest of (a) the date of death, (b) the date of last known vital status, (c) the date of migration from the extended catchment area (see below), or (d) December 31, 1999. Information on current residence and vital status is obtained primarily from responses to queries sent to regional address bureaus. Information on deaths is also obtained by reviewing all death certificates for the five rural raions (regional administrative districts) in Chelyabinsk and Kurgan Oblasts through which the Techa River flows and two rural raions where many cohort members were resettled when their contaminated villages were evacuated in the 1950s. These data are supplemented by interviews with cohort members and their relatives and acquaintances carried out at the URCRM clinic in Chelyabinsk and in examinations carried out in contaminated villages. Information on migration and death in the period prior to the creation of the cohort was obtained from village-level vital statistics and taxation records. Copies of death certificates are obtained from the local vital statistics office.

The underlying and contributing causes of death are coded from the death certificates by trained URCRM staff using 9th revision of the ICD codes (*12*). A comparison between autopsy findings and causes of death for 182 cohort members indicated agreement in 90% of the deaths (*6*). Cause of death is coded as unknown if the death certificate has not been found.

Until recently, the original catchment area for ETRC mortality follow-up included the 41 contaminated riverside villages and the villages to which cohort members were evacuated in Chelyabinsk and Kurgan Oblasts. People were treated as lost to follow-up if they migrated from this catchment area. Most of these migrants moved locally to other areas in Chelyabinsk (usually Chelyabinsk City) or Kurgan Oblasts. In recent years, we have attempted to determine the vital status and cause of death for these ''local'' migrants using address bureau queries and archive searches at vital statistics offices. These successful efforts have led to extending the mortality follow-up catchment area to include all of Chelyabinsk and Kurgan Oblasts.

Because of the importance of residence histories for dose computations, URCRM collected detailed residence histories for cohort members. These histories include one or more records per person. Each record has an indicator of the place of residence (village, town, raion), period of residence, and whether the residence is included in the original catchment area or the extended catchment area or is outside the extended catchment area. When a person's residence is unknown, these gaps are also recorded. The 86% of the cohort members residing in the extended catchment area are under active follow-up, and therefore, all of their person-years are used in risk computations. On the other hand, cohort members are treated as lost to follow-up during periods in which they are known to live outside the extended catchment area or their place of residence is unknown. Table 1 summarizes the ETRC follow-up status at the end of the current follow-up period (December 31, 1999). A total of 7,023 people were lost to follow-up: 2,841 extended catchment area residents and 4,182 who migrated outside the catchment area (''distant migrants''). About half of the in-area losses and 43% of migrant losses occurred after 1970, which means there are an appreciable number of person-years of follow-up for these cohort members.

Dosimetry

Residents of Techa River villages received external radiation exposures mainly from contaminated river shore and flood-plain soils and internal exposures from ingestion of radionuclides in drinking water and local foodstuffs. Systematic measurements of radioactive contamination in and near the Techa River started in the summer of 1951 (*13*). These measurements provide information on the contamination of the river water, bottom sediments, flood-plain soils, vegetation, fish, milk and other foodstuffs, and external γ-ray exposure rates. At the same time, some individual data on the conditions of contact with the contaminated river (the distance of the house from the water's edge, the source of drinking water, fishing, etc.) were also collected and radiometric measurements of bioassay and autopsy samples were performed.

Since ^{90}Sr was the main contributor to the internal exposure, an extensive program of *in vivo* measurements of ^{90}Sr content in teeth was begun in 1959. Whole-body counting for ^{90}Sr and ^{137}Cs has been performed since 1974. At present, about one-third of the cohort members have at least one ^{90}Sr measurement. These data form an objective basis for dose reconstruction efforts. The initial dose estimates, which were used in the first evaluation of cancer mortality risks in the original Techa River Co-

hort (*3*), were crude and involved a number of simplifying assumptions (*2*). The dose estimates were based solely on the village in which the persons received their major exposure and time patterns of dose accumulation were not considered; a 5-year period (1950–1955) of soft tissue dose accumulation and 25-year period (1950–1975) of bone marrow dose accumulation were assigned to all cohort members regardless of residence history or vital status. Only three radionuclides (^{90}Sr, ^{89}Sr and ^{137}Cs) were considered in the internal dose calculations, and the parameters used in the external dose calculations were taken from early reports that had focused on critical groups of residents for radiation protection purposes and thus were based on assumptions that tended to maximize dose estimates. In the early 1990s, dose estimates were modified to take into account the temporal pattern of ^{90}Sr accumulation and person-specific periods of dose accumulation. These estimates, which were used in analyses of cancer mortality risks through 1989 (*14*), represented only a limited improvement on the initial estimates.

The analyses in this paper are based on the newly developed TRDS-2000 dose estimates (*8, 9, 13, 15–18*). Improvements in TRDS-2000 are the result of (1) re-evaluation of all measurements of exposure rates near the shoreline and in the living areas, (2) changes in age-specific behavioral patterns based upon a re-examination of survey data on the amount of time spent near the river and in other locations, and (3) development (*15*) of a river model to describe the dependence of radionuclide concentrations in water and bottom sediments of the Techa River distance from the release site in 1949–1951 prior to the beginning of systematic measurements.

TRDS-2000 incorporates computation of internal dose estimates for additional short-lived fission products (^{85}Zr, ^{85}Nb, ^{106}Ru, ^{103}Ru, ^{141}Ce and ^{144}Ce) (*9*), models the decreases over time in exposure rates downstream from the point of release, takes account of village-specific exposure-rate measurement data to calculate a household-weighted average value of residence area-to-river bank exposure rates, and uses updated information on the average amount of time spent near the river at various ages. The new dosimetry provides dose estimates for various organs and tissues, including red bone marrow, bone surface, small intestine, stomach, upper and lower large intestine, uterus, ovaries and testes.

TRDS-2000 provides ''individualized'' dose estimates for each cohort member. The individualizations in TRDS-2000 are: (a) use of age-dependent parameters of internal and external exposure, (b) use of detailed residence histories for the full follow-up period, and (c) termination of dose accumulation at a person's date of migration from the catchment area, date of the last known vital status, or the end of follow-up, whichever occurs first. However, they do not take account of the precise location of individual residences within villages or detailed lifestyle patterns. Detailed information on TRDS-2000 including basic equations for dose computation, age dependences of parameters used for external and internal dose computations, and examples of individualized dose estimates and their uncertainties, as well as dose distributions for the entire ETRC, has been provided elsewhere (*8, 9, 18*).

Solid cancer analyses were based on stomach dose. This choice was made because stomach dose is similar to absorbed doses in the lung and other soft tissues. The primary exceptions are the intestines, which receive higher doses than most other soft tissues as a result of exposure to radiostrontium and other short-lived radionuclides with poor intestinal absorption. In addition, stomach cancer is the most common cause of cancer death. On average about 75% of the dose to the stomach is due to external exposure while the remainder is a result of the ingestion of radiocesium. Stomach dose estimates range up to 0.45 Gy with a mean (median) of 0.03 (0.005) Gy.

Leukemia analyses are based on red bone marrow dose estimates. On average 92% of the marrow dose is due to internal β-particle emitters. Red bone marrow dose estimates are as large as 2 Gy with a mean (median) of 0.30 (0.21) Gy.

The TRDS-2000 system provides annual dose estimates for each year from the later of January 1, 1950 or date of initial migration into an exposed village through the earliest of the end of follow-up or December 31, 1999. Cumulative dose to the stomach and other soft tissues are essentially unchanged after 1960, while red bone marrow doses increase throughout the follow-up period. Cumulative dose estimates at any specified time are computed as the sum of annual total (internal plus external) dose estimates with linear interpolation within the final relevant year.

Data Organization and Statistical Methods

The information available for each cohort member included gender, ethnicity, date of birth, date of arrival on the Techa, year of migration from the original catchment area, year of migration to more distant areas, date of last known vital status, the cause of death for deceased cohort members, and individualized estimates of cumulative dose (internal plus external) at the end of each year of follow-up. We considered follow-up from the latest of the date of entry into the catchment area or January 1, 1950, through the minimum of the date of death or last known vital status, migration from the catchment area, and December 31, 1999.

The risk estimates are based on detailed cross-classifications of person-years and case counts based on the individual data. The factors defining these cross-classifications included gender, ethnicity, period of entry into the catchment area (<1950, 1950–1952, or 1953–1960), Oblast at time of initial exposure, age at entry (5-year groups up to age 70 and 70 or more) defined as age in 1950 for cohort members residing in the catchment area on January 1, 1950, attained age (five groups up to age 80 and 80–110), time since arrival in the catchment area, local migration, and lagged cumulative dose. Local migration and lagged cumulative dose are time-dependent factors. As mentioned above, the person-year computations make full use of the individual time-dependent residence history information. People are not considered to be at risk when they are known to reside outside of the extended catchment area or their place of residence is unknown.

In computing cumulative doses, we assumed that the dose rate was uniform throughout each year with the annual rate equal to the increase in the cumulative dose for that year. The dose categories used include a zero-dose category and 15 additional categories defined by cutpoints at 2, 4, 8, 10, 50, 75, 100, 150, 200, 250, 300, 500, 750 and 1000 mGy. Since none of the current dose estimates exceed 500 mGy, there are only 13 stomach dose categories.

To allow for a minimum latent period, solid cancer rates were classified using lagged cumulative doses with lags of 5 years for the stomach doses used in the solid cancer analyses and 2 years for the red bone marrow doses used in the leukemia analyses. For a person at risk at time t, the n-year lagged dose was computed as the cumulative dose at time $t - n$.

Cancer death rates were analyzed using simple parametric excess relative risk (ERR) models. The basic ERR model for age-specific death rates can be written as

$$\lambda(a, d, z) = \lambda_0(a, z_0)[1 + \rho(d)\varepsilon(z_1)],$$

where a is age at death, d is dose (in Gy), z_0 represents other factors (such as sex, birth cohort, ethnicity or time) that can modify the baseline rates (λ_0), and z_1 represents factors (such as sex, age at entry, age at death, or ethnicity) that might modify the ERR.

The excess risk was described as a product of a dose–response function $\rho(d)$ and an effect modification function $[\varepsilon(z_1)]$. The dose–response function was generally taken as a linear function of dose ($\beta_1 d$). Tests for nonlinearity in the dose response are based on comparison of the linear model and linear-quadratic models ($\beta_1 d + \beta_2 d^2$). Log-linear models were used to describe radiation effect modifiers.

We briefly consider excess absolute rate (EAR) models of the form

$$\lambda(a, d, z) = \lambda_0(a, z_0) + \rho(d)\varepsilon(z_1),$$

where the effect modification $[\varepsilon(z_1)]$ involves a power of age and possibly other factors.

Once a model has been fitted, it is possible to estimate the number of baseline and radiation-associated cases by summing the product of the person-years and fitted baseline $[\lambda_0(a, z_0)]$ or excess rates $[\lambda_0(a, z_0)\rho(d)\varepsilon(z_1)$ for an ERR model or $\rho(d)\varepsilon(z_1)$ for an EAR model)] over all of the cells in the rate table used for the analyses.

TABLE 2
Distribution of Person-Years and Cancer Deaths in the Extended Techa River Cohort by Selected Factors

		Deaths		
			Leukemia	
	PY	Solid cancer[a]	Any	CLL[b]
Gender				
Male	352,877	931	24	6
Female	512,935	911	37	6
Entry age				
0–9	176,843	67	9	2
10–19	219,156	239	16	0
20–39	308,397	764	21	7
40+	161,416	772	15	3
Attained age				
0–39	355,839	60	15	0
40–59	314,031	604	20	2
60–79	173,113	1,041	23	9
80+	22,829	137	3	1
Entry period				
1950–1952	751,009	1,588	56	11
1953–1959	114,802	254	5	1
Ethnicity				
Slav	661,807	1,462	43	9
Tartar/Bashkir	204,005	380	18	3
Total	*865,812*	*1,842*	*61*	*12*

[a] Excludes 18 bone cancer deaths.
[b] CLL = chronic lymphocytic leukemia (ICD-9 code 204.1).

Parameter estimates were determined using Poisson regression maximum likelihood analyses of rates in the detailed rate tables described above. Significance tests and confidence intervals were determined directly from the likelihood. The person-year table was created and the models were fitted using the EPICURE software (*19*).

Log baseline rates for solid cancers were modeled as sex-specific quadratic functions of log attained age with a sex-dependent birth cohort effect and a sex-independent effect for ethnicity and for Oblast. (The motivation for inclusion of this Oblast effect is discussed below.)

The Techa River cohort study has been reviewed and approved by the URCRM IRB.

TABLE 3
ETRC Solid Cancers 1950–1999 by Dose Category[a]

Stomach dose (Gy)	Person years	Cases	Expected	Excess
<0.01	629,830	1,287	1,278.8	4.3
−0.05	158,218	346	344.3	7.8
−0.1	19,113	40	37.6	2.3
−0.2	29,477	71	64.5	7.8
−0.3	8,688	25	15.9	3.7
0.3+	20,486	73	54.9	20.1
Total	865,812	1,842	1,796	46

[a] Estimates of the number of expected and radiation-associated excess cases are based on the fitted excess relative risk model with a linear dose response and no effect modification.

RESULTS

The analyses in this report are focused on deaths from solid cancers (ICD-9 codes 140–199) other than bone cancer (ICD-9 code 170) and from leukemia (ICD-9 codes 204–208). Bone cancers were excluded from the solid cancers because of the potential effects of ^{90}Sr exposure on these cancers. Between 1950 and 1999, 1842 solid cancer deaths (not including 18 bone cancer deaths) and 61 leukemia deaths occurred. Table 2 presents information on the distribution of deaths and person years by gender, age, age at entry, ethnicity and initial exposure period.

Solid Cancer

1. Baseline risks

In addition to effects of age, gender, ethnicity and birth cohort, the baseline solid cancer rate model used in these analyses includes a standardized mortality ratio (SMR)-like parameter for residence in Kurgan Oblast. Estimation of a solid cancer SMR for Kurgan residents reveals significantly lower ($P < 0.001$) age-specific death rates in Kurgan than in Chelyabinsk. Allowing for a linear dose response, the baseline SMR for Kurgan relative to Chelyabinsk is 0.74 (95% CI 0.66; 0.83) and is almost the same (0.72) without allowance for dose effects. All-cause age-adjusted death rates for Kurgan are about 5% greater than those for Chelyabinsk and, as this suggests, non-cancer death rates in Kurgan are significantly higher than those in Chelyabinsk (SMR 1.11, 95% CI 1.07; 1.16, $P < 0.001$). Since the proportion of deaths with unknown cause is slightly greater (12%) for Chelyabinsk cohort members than for the Kurgan members (10%), this difference cannot be explained by differences in the probability of determining the cause of death. Comparison to Russian national rates (with a simple allowance for unknown cause of death in the ETRC) also suggests that baseline solid cancer death rates may be low for Kurgan residents and high for Chelyabinsk residents, with SMRs of 0.85 and 1.1 for Kurgan and Chelyabinsk, respectively. While the reasons for the Oblast differences are unclear, it seems unlikely that they are related to radiation dose. Nevertheless, since doses received by cohort members in Kurgan Oblast are typically much lower than those received by cohort members in Chelyabinsk Oblast, failure to allow for these differences will lead to biased risk estimates that are more than 50% greater than the adjusted estimates.

As one would expect based on data from many populations, baseline rates for women are considerably lower than those for men after middle age. Baseline rates for the Tartar/Bashkir group are estimated to be about 80% of those for Slavs.

2. Radiation risk estimates

Table 3 presents estimates of the number of radiation-associated solid cancer deaths in the ETRC extended catch-

TABLE 4
Solid Cancer Risk Estimates

Model/parameter	Estimate	95% CI
Linear (ERR/Gy)	0.92	(0.2; 1.7)
	$P < 0.001$	
Linear-quadratic		
Linear	0.85	
Quadratic	0.18	
	$P = > 0.5$ (non-linearity)	

ment area based on a linear dose–response model without effect modification adjusted for effects of age, gender, ethnicity, birth cohort, and Oblast on the baseline rates. It is estimated that about 2.5% of the solid cancer deaths are related to radiation exposure from the Techa River.

As shown in Table 4, there is a highly significant ($P < 0.001$) dose response with a linear ERR estimate of 0.92 per gray (95% CI 0.2; 1.7). The low-dose slope for a linear-quadratic model is almost the same as the linear model risk estimate, and there is no evidence of significant non-linearity ($P > 0.5$).

Figure 1 compares the fitted linear and linear-quadratic dose–response functions with non-parametric dose-category-specific ERR estimates.

Table 5 describes results concerning effect modification. While the ERR for women is estimated to be about 70% greater than that for men, the difference is not statistically significant ($P > 0.5$). There is some suggestion that the ERR is increasing with increasing age at first exposure ($P = 0.08$) or attained age ($P = 0.03$). This age–time pattern seems strikingly different from that seen in the atomic bomb survivors (*20*) or Mayak workers (*21*). There is also some indication of higher risks per unit dose among the non-Slav ethnic groups.

Since the dose to the colon tends to be considerably higher than that to other organs, there is a concern that inclusion of colorectal cancers in analyses based on stomach/average soft tissue doses might lead to appreciable upward bias in the risk estimate. However, the risk estimate is essentially unchanged when estimates are based on solid cancers other than colorectal cancers (ERR per Gy = 0.9, 95% CI 0.2; 1.7).

We also carried out some analyses to assess the impact of changes in the catchment area. Exclusion of local (Chelyabinsk and Kurgan) migrants (that is, use of the original catchment area) tends to increase the ERR estimates somewhat (1.4, 95% CI 0.4; 2.5). On the other hand, exclusion of late entrants (that is, restriction to the original Techa River Cohort) results in no change in the risk estimates (0.9, 95% CI 0.2; 1.8).

The ETRC data can be described equally well using a simple EAR model in which the excess rate increases with attained age. The estimated EAR at age 70 is 70.5 cases per 10,000 PY per gray (95% CI 25; 118), and the increase with age is proportional to age to the power 4.5 (95% CI 2.0; 8.8). There is no indication that the EAR depends on gender, ethnicity or age at entry. Because cause of death is unknown for about 11% of the deaths in the cohort this EAR estimate is biased downward. Assuming that the distribution of causes of death among those with unknown cause is similar to that seen for deaths with known cause, the EAR estimate is likely to be about 10% too low.

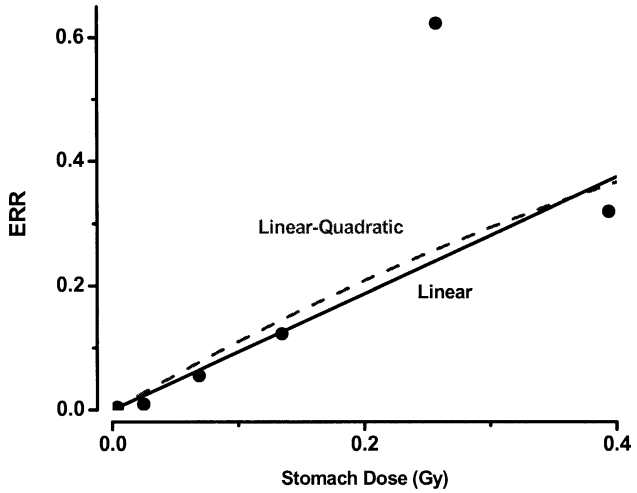

FIG. 1. ETRC solid cancer dose response.

Leukemia Risk Estimates

1. Baseline risks

There are 49 non-CLL leukemia deaths and 12 CLL deaths among ETRC cohort members. Furthermore, as indicated below, a significant fraction of the non-CLL leukemia deaths appear to be associated with the radiation exposure. Therefore, these data do not support the development of richly parameterized baseline risk models. In de-

TABLE 5
Solid Cancer Risk Effect Modification on the Excess Relative Risk

Gender	Male	Female	Female:male ratio
	0.6[a]	1.2	1.9
			(0.3 inf)[b]
			$P > 0.5$
Age at entry	10 years	40 years	Percentage increase per decade
	0.4	1.1	33%
			(−6%; +100%)
			$P = 0.08$
Attained age	40 years	70 years	Power of age
	0.2	1.2	3.4
			(0.3; 7.9)
			$P = 0.03$
Ethnicity	Slav	Tartar	Tartar:Slav ratio
	0.6	2.9	4.7
			(0.98; >100)
			$P = 0.052$

[a] ERR/Gy.
[b] 95% confidence interval.

TABLE 6
ETRC Non-CLL Leukemias 1950–1999 by Dose Category[a]

Marrow dose (Gy)	Person years	Cases	Expected	Excess
0	54,541	0	1.2	0.0
−0.01	91,876	4	1.9	0.0
−0.05	68,143	1	1.4	0.2
−0.1	79,142	1	1.6	0.8
−0.2	170,966	10	3.6	3.6
−0.5	245,331	15	5.1	10.3
−1	132,790	13	2.8	12.4
1+	23,022	5	0.5	3.6
Total	865,811	49	18.1	30.9

[a] Estimates of the number of expected and radiation-associated excess cases are based on the fitted excess relative risk model with a linear dose response and no effect modification.

veloping baseline risk models for these analyses, we considered effects of age, gender, ethnicity and birth cohort. Rates for all types of leukemia combined are well described by a simple model in which the log rate increases as a quadratic function of log age at death with no indication of dependence on sex, ethnicity or birth cohort. Neither age nor any other factors appeared to have a significant effect on non-CLL baseline risks, while CLL baseline rates increase markedly with age. However, we decided to allow for a baseline age dependence of the same form as that used for the all-leukemia baseline rate model. We were not able to find appropriately detailed Russian national rates for CLL and non-CLL leukemia, so no SMR analyses were made. In contrast to solid cancers, there is no indication that non-CLL baseline rates differ markedly for the Kurgan and Chelyabinsk groups (Kurgan SMR is 1.04 with $P > 0.5$).

2. Radiation risk estimates

Dose–response analyses were based on 2-year lagged bone marrow dose estimates. A significant dose response is seen for all leukemias as a group ($P < 0.001$). The estimated ERR per gray in a linear dose–response model is 4.2 (95% CI 1.2; 13). There is no indication of a dose response for CLL ($P > 0.5$). The linear ERR estimate is 0.5 (95% CI < -0.8; 9). In view of this result and the general observation that CLL risks have little or no association with radiation exposure in other populations, we focus on results for non-CLL leukemias.

Table 6 presents the observed numbers of non-CLL leukemia deaths by dose category along with estimates of the number of expected and radiation-associated excess cases based on a simple linear dose–response model with no effect modification. We estimate that about 63% of the leukemia deaths are associated with radiation exposure.

As indicated in Table 7, there is strong evidence of a dose response ($P < 0.001$) for non-CLL leukemia with an estimated linear ERR per Gy of 6.5 (95% CI 1.8; 24). We found no evidence of significant non-linearity ($P > 0.5$), and the estimated low dose slope in a linear-quadratic model is virtually identical to that for the linear model.

TABLE 7
Non-CLL Leukemia Risk Estimates

Model/parameter	Estimate	95% CI
Linear (ERR/Gy)	6.5	(1.8; 24)
	$P < 0.001$	
Linear-quadratic		
Linear	6.0	
Quadratic	0.5	
	$P = >0.5$ (non-linearity)	

Figure 2 compares the fitted linear and linear-quadratic dose–response functions with dose category-specific ERR estimates.

As with the solid cancer data, there is a suggestion ($P = 0.1$) of an increase in the ERR per gray with increasing age at entry but no indication of variation in the ERR with gender, ethnicity, attained age, or time since exposure. However, in view of the small number of leukemia cases, these tests lack the statistical power to provide useful effect modification estimates.

Similar to our solid cancer results, a simple EAR model describes the leukemia excess risk as well as the ERR models presented above. In an age-dependent EAR model, the estimated excess rate at age 70 is 2.9 deaths per 10,000 PY per gray (95% CI 0.8; 4.4). In this model, the risk increases in proportion to age to the power 1.7 (95% CI −0.4; 3.5), but age was only marginally significant ($P = 0.1$), and the estimated age-constant EAR is 1.2 cases per 10,000 PY per gray (95% CI 0.6; 2.0). The fit of this simple model was improved significantly ($P = 0.03$) by the addition of an age-at-entry effect. The best fit was obtained for an EAR model in which the excess rate varied with age at entry with no dependence on attained age. With this model, the

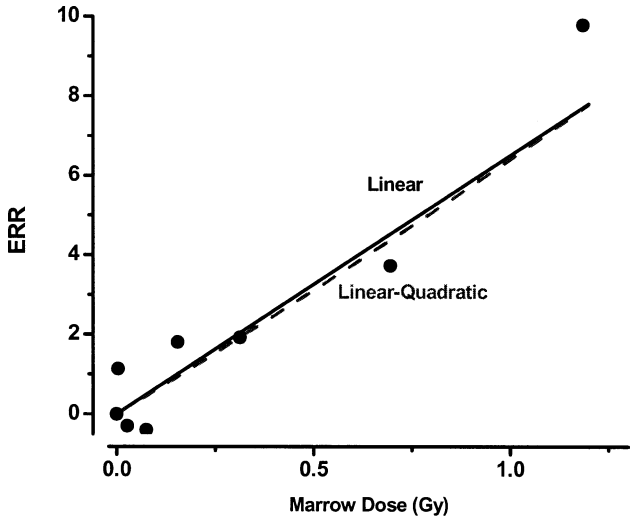

FIG. 2. ETRC non-CLL leukemia dose response.

excess rate for initial exposure at age 25 is 1.7 cases per 10,000 PY per gray (95% CI 0.9; 2.4), and the excess rate increases by 34% with each decade increase in the age at entry (95% CI 4%; 60%).

DISCUSSION

The ETRC provides a unique opportunity to estimate radiation risks based on the long-term follow-up of a large, unselected population consisting of men and women of all ages who received significant internal and external radiation exposures at low dose rates. The current analyses improve on earlier summaries because they are based on an extended follow-up period, with significant improvements in the quality of follow-up, and the best available dose estimates. Follow-up quality has been improved by more complete ascertainment of vital status and cause of death and by inclusion of follow-up data for over 5,000 cohort members who moved from the original study area to other areas in Chelyabinsk or Kurgan Oblasts. The new dose estimates represent a major advance over previous estimates in that they incorporate improvements in models for transport of radioactive material down the Techa River, take more complete account of individual residence histories, and are based on more realistic assumptions about distance from the river banks and flood plains at the time of exposure.

Our results provide clear evidence of elevated solid cancer and leukemia mortality risks and a strong dose–response relationship associated with exposure to radiation from the contaminated Techa River. Using individualized dose estimates based on the TRDS-2000, we have been able to estimate the slope of the dose response for both solid cancer and leukemia, and we found no indications of significant curvature.

Precise inference about radiation effect modifiers is not possible due to the small number of radiation-associated cases in the cohort. However, gender differences in the solid cancer ERR (females greater than males) are consistent with what one expects based on the atomic bomb survivors (*20*) and many other exposed populations (*21–23*). There are suggestions in these data that the solid cancer ERR increases with increasing age at first exposure or attained age (age at death) and that the leukemia ERR increases with increasing age at first exposure. These patterns appear to contradict what one would expect on the basis of the atomic bomb survivors (*20, 24*) and mechanistic considerations (*25–28*), but some analyses of U.S. nuclear workers have suggested similar general patterns (*29, 30*). To try to better understand these unexpected temporal patterns, we performed some more detailed descriptive analyses. We began by looking at the temporal patterns of the ERR in three age-at-entry groups: 0–19, 20–39, and 40+. Since the results for the two youngest age groups did not differ, we combined them into one group of persons <40 years old at first exposure. In those exposed later in life, the ERR decreased rapidly with increasing attained age. In contrast, the ERR increased rapidly with attained age for those exposed under age 40. These differences were statistically significant. For those initially exposed after age 40, with a total cumulative dose of 200 mGy, solid cancer risks are (rather imprecisely) estimated to be increased by about 70% at age 60 and only 20% at age 70. For those with a 200-mGy exposure earlier in life, solid cancer risks are estimated to be increased by 12% and 40% at attained ages of 60 and 70 years, respectively. It is difficult to understand or explain these findings. While younger cohort members were more likely to be lost to follow-up than older cohort members, the proportion lost to follow-up does not depend on dose either overall or within age-at-entry groups. Thus selection bias would seem to be an unlikely explanation for these findings. Another possible source of bias involves dose- and age-related differences in the likelihood of reporting solid cancer as the primary cause of death. For such a reporting bias to lead to the temporal patterns seen in these data, during the first decades of follow-up, younger people with high doses would have to be less likely to have solid cancers reported on their death certificate than their low-dose peers, while among people who were older at initial exposure, the opposite pattern would need to be seen. It is difficult to see how this could be the case, especially since the physicians filling out death certificates had no knowledge of individual doses and little if any knowledge of exposure status. The next decade will provide important new information on the temporal pattern of the excess risk among persons exposed as children or young adults.

Despite its strengths, the ETRC currently has a number of limitations that have an impact on its usefulness as a source of precise quantitative radiation risk estimates. While there have been significant improvements in follow-up, 14% of the cohort members are lost to follow-up as a result of migration from Chelyabinsk and Kurgan Oblasts, and information on vital status is unavailable for almost 11% of the remaining cohort members. These two groups contribute about 13% of the total person-years in this study. Furthermore, the cause of death is unknown for about 13% of deceased cohort members. Taken together, these factors decrease the effective size of the cohort by about 35% and raise the possibility of unknown biases related to loss to follow-up. It is certainly possible for selection or other biases to lead to incorrect inferences about exposure effects or even dose response; however, for this to occur in dose–response analyses such as these, the selection effects would need to exhibit rather complex joint dependence on dose and other factors. In particular, gender or age differences in the rates of loss to follow-up in and of themselves should not lead to biased risk estimates in this population.

There are also concerns that the frequency of diagnostic X-ray examinations, and hence medical radiation dose, may be correlated with cohort members' radiation exposure from Mayak releases. To address this, medical records at URCRM are being abstracted to obtain information on medical radiation exposure. Preliminary analyses have been

conducted in which risk estimates were adjusted using two readily available surrogates for diagnostic X-ray examinations: the number of in-patient stays in the URCRM clinic and diagnoses with, or with suspicion of, chronic radiation syndrome. These analyses indicate that adjustment for number of hospitalizations did not change the solid cancer or leukemia radiation risk estimates. The adjusted solid cancer ERR was 1.0 compared with 0.92 without the adjustment, and the adjusted non-CLL leukemia ERR was 6 compared with 6.5 without the adjustment. Analyses adjusting for suspicion of chronic radiation syndrome did not affect radiation risk estimates either. These results suggest that the current risk estimates are unlikely to be seriously biased as a result of failure to account for diagnostic medical X-ray exposures. As information becomes available, we will also consider the impact of additional radiation exposure to residents of upper Techa villages from Mayak's routine and accidental airborne releases during the 1950s. We do not expect these changes to have a large impact on risk estimates.

TRDS-2000 has been documented extensively in peer-reviewed articles (*8, 9, 18*) and evaluated by various independent groups. Although the source term used in TRDS-2000 is based on materials issued by Mayak (*31, 32*), a Mayak scientist recently suggested that the contribution of short-lived radionuclides to the total releases into the Techa River in 1949–1951 were much greater than estimated using TRDS-2000 (*10, 11, 33*). In an attempt to resolve this issue, an international group of scientists met to review TRDS-2000 in 2003. In their final report, the basic TRDS-2000 approach was endorsed, but collaborative efforts with Mayak experts were recommended to resolve the contentious source-term issues as well as other dosimetry issues (*34*).

Thus the nature of the source term is currently being reviewed, and changes may be made that result in a higher contribution of short-lived radionuclides. Such changes would lead to some change in external dose estimates and to an increase in internal dose estimates for the bone marrow (due to short-lived ^{89}Sr) and the gastrointestinal tract (due to short-lived radionuclides with poor intestinal absorption). Risk estimates for leukemia as well as for solid cancer would be reduced somewhat by such changes.

The assessment of the validity of ETRC external dose estimates can be done by comparing a sample of model-based doses with results obtained using retrospective dosimetry or biodosimetric methods. To date, validation studies in Metlino, the settlement with the highest external exposures, have been completed (*35–37*), and the results are consistent with TRDS-2000 dose estimates. Further validation studies including studies based on samples from locations downstream from Metlino are now under way.

The mortality risk estimates in this paper, ERRs of 0.92 for solid cancer excluding bone cancers, 4.2 for leukemia including CLL, and 6.5 for leukemia excluding CLL, are somewhat higher than those suggested for this cohort in earlier publications. Including the 18 bone cancer deaths has no effect on the solid cancer risk estimate (it changes the ERR by 0.01). The first widely available cancer mortality risk estimates for the original Techa River Cohort (excluding late entrants) are based on follow-up through 1982. Kossenko (*14*) reports an ERR estimate of 0.65 based on 740 solid cancer deaths excluding bone sarcoma, while Kossenko and Degteva (*3*) provide a total leukemia (including CLL) ERR estimate of 3.2 based on 27 cases. The crude dose estimates used for computing these risks tended to be overestimates because they did not properly account for residence history. A recently completed case–control study of 63 ETRC non-CLL leukemia cases reported an ERR estimate (based on the fitted odds ratio) of 3.6, and when the 20 CLL cases were included, the estimate was reduced to 2.5 (*38*). Doses used for this study were based on TRDS-1996, which made limited use of residence history information but, as was the case with earlier estimates, made assumptions that tended to bias external dose estimates upward (*39*) The primary reason for the increased risk estimates in our current analysis is the lower dose estimates resulting from the use of an improved dosimetry system (TRDS-2000). Other factors that might contribute to the change in risk estimates are the longer follow-up, the larger cohort, and the more complete ascertainment of deaths.

It is widely known that radiation risks tend to vary with age at exposure, gender and, emerging evidence suggests, attained age. Thus, while it is difficult to make meaningful comparisons of simple summary risk estimates, comparisons that crudely take these factors into account are useful. The solid cancer ERR estimate for the ETRC is about 50% higher than the most recent sex-averaged estimate for atomic bomb survivors at age 65 (which is the mean age at death from cancer in the ETRC) after exposure at age 25 (which is the mean age at initial exposure in the ETRC).

Comparison of leukemia risks with those from the atomic bomb survivor cohort is even more difficult since those data are usually described in terms of excess rates rather than excess relative risks and the excess risks exhibit complex variation with age at exposure and time. CLL is a rare disease in Japan, and the few CLL cases in the atomic bomb survivor studies do not appreciably affect the risk. Thus the atomic bomb survivor leukemia risk estimates should be considered as risks for leukemia excluding CLL. Based on the most recent publicly available atomic bomb survivor leukemia mortality data (*40*), a simple estimate of the leukemia ERR per sievert is 4. It should be noted that follow-up for the A-bomb survivors begins 5 years after exposure, whereas follow-up begins immediately after exposure in this study. The current excess relative risk estimates for the ETRC are somewhat higher than those seen in the atomic bomb survivor studies, but in view of the uncertainties of the estimates for the two cohorts, the results cannot be said to differ. In addition, while the atomic bomb survivor data appear to suggest a non-linear dose response,

there is little evidence of non-linearity in the ETRC leukemia dose response.

In view of the dosimetric uncertainties noted above, comparisons between the radiation-associated cancer risks for atomic bomb survivors (who received acute external exposures) and ETRC members (who received protracted low-dose-rate internal and external exposures) cannot be conclusive at this time. Without allowance for the impact of uncertainties in ETRC dose estimates, the atomic bomb survivor risk estimates are included in the 95% confidence intervals for the ETRC estimates. If uncertainties in ETRC dose estimates are taken into account, the confidence intervals for the ETRC risk estimates will be even wider. Thus the current data do not indicate that the cancer mortality risks differ significantly in the two populations.

The last few years have seen major progress in the quality and completeness of the ETRC mortality follow-up as well as significant advancements in dosimetry. Work on both of these aspects of this study is continuing. Our current analyses clearly demonstrate a significant dose response for both solid cancers and non-CLL leukemia and add important information on radiation risks associated with protracted exposures. Over the next few years, we expect to improve risk estimates with more complete characterization of uncertainties and possible biases in these estimates.

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